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Health and Environmental Effects Profile for Stirofos

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR STIROFOS

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OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
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16. ABSTRACT

The Health and Environmental Effects Profile for stirofos was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Stirofos has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for stirofos is 2.4×10^{-2} (mg/kg bw/day)$^{-1}$ for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	2
1.3.	PRODUCTION DATA	2
1.4.	USE DATA	3
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	4
2.1.	WATER	4
2.2.	AIR	5
2.3.	SOIL	6
2.4.	PERSISTENCE IN PLANTS	7
3.	EXPOSURE	10
3.1.	WATER	10
3.2.	FOOD	10
3.3.	INHALATION	10
3.4.	DERMAL	11
4.	PHARMACOKINETICS	12
4.1.	ABSORPTION	12
4.2.	DISTRIBUTION	12
4.3.	METABOLISM	13
4.4.	EXCRETION	16
5.	EFFECTS	18
5.1.	CARCINOGENICITY	18
5.2.	MUTAGENICITY	19
5.3.	TERATOGENICITY	21
5.4.	OTHER REPRODUCTIVE EFFECTS	21
5.5.	CHRONIC AND SUBCHRONIC TOXICITY	21
5.6.	OTHER RELEVANT INFORMATION	23
6.	AQUATIC TOXICITY	25
7.	EXISTING GUIDELINES AND STANDARDS	26
7.1.	HUMAN	26
7.2.	AQUATIC	26
8.	RISK ASSESSMENT	27
9.	REFERENCES	29
APPENDIX:	LITERATURE SEARCHED	36

LIST OF TABLES

No.	Title	Page
2-1	Persistence of Stirofos on Plants After Indoor Treatments . .	9
5-1	Mutagenicity Data for Stirofos.	20
5-2	Acute Lethal Data for Stirofos.	24

LIST OF FIGURES

No.	Title	Page
4-1	Possible Metabolic Pathway of Stirofos in Animals	15

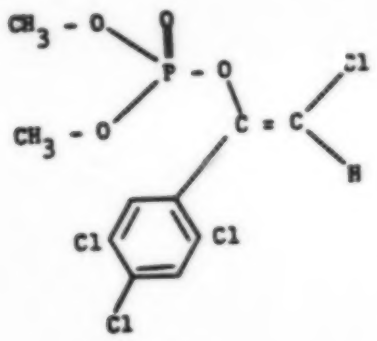
LIST OF ABBREVIATIONS

bw	Body weight
DNA	Deoxyribonucleic acid
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
ppm	Parts per million
TWA	Time-weighted average

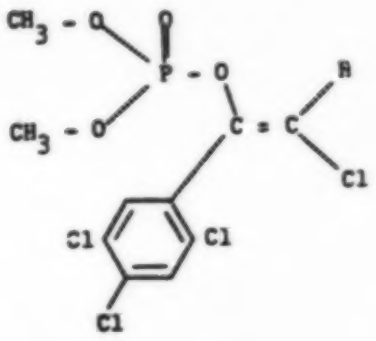
1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Stirofos is the common name for 2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate. It is also commonly named tetrachlorvinphos. Current Chemical Abstract usage is 2-chloro-1-(2,4,5-trichlorophenyl)ethenyl dimethyl phosphate. Other chemical synonyms include dimethyl-1-(2,4,5-trichlorophenyl)-2-chlorovinyl phosphate and 2,4,5-trichloro-alpha-(chloromethylene)-benzyl di-methylphosphate. Stirofos was introduced in 1966 by the Shell Development Company under the code number "SD 8447" and the trademark "Gardona" (BCPC, 1977). Other synonyms for stirofos or its commercial formulations include Rabon, Rabond, Rol, stirophos, Gardcide, Dietreen, CVMP, Appex, NCI-C00168 and ENT 25841. The commercial stirofos product is a mixture of the trans- and cis-isomers. The trans-isomer comprises 94-98% of the product (Beynon et al., 1973; BCPC, 1977). The structural and molecular formulae for stirofos are as follows:



Trans-Isomer



Cis-Isomer

Empirical formula: $C_{10}H_9Cl_4O_4P$

Molecular weight: 366.0

The Chemical Abstract Service (CAS) Registry number for the mixed isomers is 961-11-5. The CAS number for the cis-isomer is 22248-79-9 and for the trans-isomer is 22350-76-1.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Stirofos (98% cis-isomer) is a white to off-white crystalline solid at room temperature (BCPC, 1977; Ouellette and King, 1977). Selected physical properties are listed below:

Melting point:	95-97°C	(BCPC, 1977)
Vapor pressure at 20°C:	4.2×10^{-6} mm Hg	(Ouellette and King, 1977)
at 25°C:	1.5×10^{-6} mm Hg	(BCPC, 1977)
Solubility at 20°C:		(BCPC, 1977)
water	11 ppm	
acetone	<200 g/kg	
chloroform	400 g/kg	
dichloromethane	400 g/kg	
xylene	<150 g/kg	
Soil adsorption coefficient, K_{OC}: (calculated from water solubility)	1170	(Kenaga, 1980)
Bioconcentration factor: (calculated from water solubility)	160	(Kenaga, 1980)

Stirofos is thermally stable to 100°C (BCPC, 1977). It is more susceptible to alkaline hydrolysis than to acid hydrolysis (Beynon et al., 1973).

1.3. PRODUCTION DATA

Stirofos is prepared by the reaction of trimethyl phosphite with 2,2,2',4',5'-pentachloroacetophenone (BCPC, 1977).

The only domestic producer of stirofos is Shell Chemical Company in Mobile, AL (SRI, 1983; USITC, 1983). Current production figures are not available. The capacity of Shell's facility to produce stirofos is reported to be one million pounds annually (SRI, 1976).

1.4. USE DATA

Stirofos is used as a selective insecticide to control lepidopterous, dipterous and coleopterous pests of fruit, rice, cotton, maize, vegetables and tobacco (BCPC, 1977). It is also used to control houseflies and flies in dairies and livestock barns, as a control of chicken mites, lice and screwworms, as a control against pests of stored products, and as a moth-proofing agent (BCPC, 1977; Ouellette and King, 1977).

In 1975, 0.1 million pounds of stirofos were domestically consumed to control pests in livestock and poultry applications (SRI, 1976).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

The fate of stirofos in water will depend on its ability to undergo chemical, biological and photochemical reactions and evaporate or adsorb to sediments. Selected hydrolysis rates for stirofos have been determined and are summarized below:

Temperature, °C	pH	Half-Life, (hours)	Reference
38	9.1	37	Whetstone et al., 1966
50	3	1300	Beynon et al., 1973
	7	1060	
	10.5	80	
85	3	12	Beynon et al., 1973
	7	8	
	10.5	<1	

The hydrolysis data available indicate that the rate of hydrolysis of stirofos is highly dependent upon pH and temperature. Alkali hydrolysis proceeds faster than acid hydrolysis and increasing temperatures appear to accelerate the hydrolysis rate. The hydrolysis data available were not produced at environmentally significant conditions of temperature (<30°C), but it can be predicted that at 25°C, the hydrolysis half-lives will be a factor of 10 slower than at 50°C, or half-lives of 13,000, 10,060 and 800 hours at pH 3, 7 and 10.5, respectively (Lyman et al., 1982).

The microbial degradation of stirofos in water has not been examined in the available literature. Beynon et al. (1973) have suggested that microbiological reactions are mainly responsible for stirofos depletion in soils. Also, data presented by Lal (1982) (Section 2.3.) indicate that microorganisms are capable of degrading stirofos. Therefore, it is possible that the microbial degradation of stirofos in the aquatic media is significant.

Beynon et al. (1973) noted that stirofos has an absorption maximum at 212 nm and absorbs very little sunlight. This would indicate that the direct photolysis of stirofos would be relatively insignificant as a degradation mechanism. However, this does not consider the potential for the photosensitized photodecomposition of stirofos.

Specific to the transport of stirofos in the aquatic media due to volatilization, runoff or sedimentation were not located in the available literature. However, the calculated K_{oc} value of 1170 (Kenaga, 1980), water solubility of 11 ppm, and vapor pressure of 10^{-6} to 10^{-8} mm Hg suggests that stirofos does not evaporate rapidly from water and probably adsorbs significantly to sediments.

Kenaga (1980) has predicted the bioconcentration factor for stirofos, based upon water solubility, to be 160. Generally, bioconcentration factors with values <1000 are considered to be unlikely to bioconcentrate strongly.

2.2. AIR

Little data specific to the fate and transport of stirofos in the atmosphere were located in the available literature cited in the Appendix. Beynon et al. (1973) have noted that stirofos has an absorption maximum at 212 nm and absorbs very little sunlight. As noted before, this would indicate that direct photolysis may be environmentally insignificant, but does not consider photosensitized degradation. Cupitt (1980) has suggested that the vapor-phase removal mechanism is reasonable only for materials with saturation vapor pressures of $<10^{-7}$ mm Hg. At 20°C, stirofos has a reported saturation vapor pressure of 4.2×10^{-6} mm Hg (BCPC, 1977; Beynon et al., 1973). This may indicate that stirofos may potentially remain strongly sorbed to particulate matter in the air. The particulate matter to which the stirofos is sorbed can be transported to water or soil media via drift,

dry deposition or wet deposition. The particulate matter may also be able to photosensitize photolysis reactions. It must be noted that these suggestions of particulate sorption and photosensitization of stirofos have not been demonstrated experimentally.

2.3. SOIL

The degradation of stirofos in soils has been studied by Beynon and Wright (1969) in the laboratory. Four soil types were tested which had the following characteristics: sandy loam (pH 7.9, 16% moisture), medium loam (pH 8.0, 19% moisture), clay loam (pH 8.0, 20% moisture) and peat (pH 6.4, 100% moisture on dry weight). The soil types were placed in a laboratory jar and given an overall ^{14}C-stirofos concentration of 13.4 ppm. The jars were tumbled to ensure mixing and stored in subdued sunlight at 15°C. After 30 days, the percentage of stirofos remaining in each soil type was as follows:

medium loam	9.0%
clay loam	3.0%
sandy loam	2.2%
peat	15.0%

In medium loam, the percentage of stirofos remaining after 8 days and 16 days was 29 and 14%, respectively. The following degradation products were identified:

(1) 2,4,5-trichlorophenacyl chloride
(2) 2,4,5-trichloroacetophenone
(3) 1-(2',4',5'-trichlorophenyl)-2-chloroethan-1-ol
(4) 1-(2',4',5'-trichlorophenyl)ethan-1-ol
(5) 1-(2',4',5')trichlorophenylethanediol
(6) dimethyl stirofos
(7) unextractables (acetone)

Excluding (7) above, compounds (3) and (4) were present in the greatest amounts after 30 days. The pathway of stirofos degradation in the soils tested occurred by hydrolysis of the P-O-C bond to give initially 2,4,5-trichlorophenacyl chloride and demethyl stirofos, followed by reactions of these two compounds involving reduction of the ketone group and reductive dechlorination.

Beynon and Wright (1969), in the above study, did not identify the mechanism (microbial, chemical, photolysis) by which the stirofos was degraded in the soils. In a later paper, Beynon et al. (1973) noted that the rate of degradation was greater than expected from hydrolysis studies, and therefore, the reactions in soil were probably mainly microbiological. Also, the mixing of the soils left little opportunity for photodegradation.

Data presented in Lal (1982) has noted that Aspergillus and Penicillium were able to grow well on malt medium containing various concentrations of stirofos and the degradation of stirofos increased as its concentration was increased. Also, stirofos had a growth-stimulating effect on Fusarium javanicum, Mucor fragilis, Mucor hiemelis and Penicullium aurantiocandidum.

Kenaga (1980) has predicted a soil adsorption coefficient, K_{oc}, for stirofos of 1170 based upon its water solubility. Compounds having a K_{oc} value >1000 are quite tightly bound to organic matter in soil and are considered immobile.

2.4. PERSISTENCE IN PLANTS

The persistence of stirofos on plants has been reported by several investigators. In addition to the soil studies discussed in Section 2.3., Beynon and Wright (1969) studied the breakdown of stirofos on various plants after indoor treatments. The plants were grown in a greenhouse and the

stirofos was topically applied by various methods at determined concentrations. The persistence results are summarized in Table 2-1. The degradation products produced by the plants were identified and found to be mainly the same as the metabolites formed in the soil as listed in Section 2.3. However, a major difference was the formation of the trans-stirofos isomer on the plants, thought to be formed by the photolytic isomerization of the cis-isomer. Beynon et al. (1973) reported that the residues of stirofos in apples under field conditions after treatment was 3.4,0.49, 0.15 and 0.06 ppm after 0, 14, 30 and >35 days, respectively.

Sundaram (1974) found that stirofos residues on white pines decreased from 4.2 ppm on day 0 to 0.17 ppm after 50 days. The stirofos was applied as an aerial spray at a rate of 1.0 lb/acre for control of white pine weevils.

Hall et al. (1973) studied the persistence of stirofos on corn and wheat held in farm storage. The grains were placed in partitioned, metal farm-storage bins that provided for treated vs. control samples. Storage and stirofos treatment was initiated during October-November 1970. Residues were periodically examined through June 1971. In the corn storage, the initial stirofos residue concentrations showed no significant reductions through the winter months (to mid-March 1971) but by June 1971, the stirofos levels remaining were ~42% of the application concentrations. In the wheat samples, from 70-100% of the stirofos residue levels sampled after application in the fall remained in June 1971.

TABLE 2-1

Persistence of Stirofos on Plants After Indoor Treatments[a]

	% Stirofos[b] Residues in Plant After Treatment After:									
	0 Days	1 Days	2 Days	3 Days	4 Days	5 Days	7 Days	11-12 Days	18 Days	39 Days
Cabbage plants	NR	50	NR	NR	NR	11.4	3.5	0.17	NR	NR
Apple leaves	NR	NR	NR	NR	NR	NR	15.9	NR	NR	NR
Apples and leaves	73	NR	34	NR	11	NR	7	6	6	3.5
Rice	83	52	NR	NR	17	NR	17	4	NR	NR

[a]Source: Beynon and Wright, 1969, Beynon et al., 1973

[b]cis-isomer

NR = Not reported

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3. EXPOSURE

3.1. WATER

The U.S. EPA STORET data base contains no data relevant to stirofos monitoring. Other pertinent data regarding stirofos monitoring for water exposure were not located in the available literature cited in the Appendix.

3.2. FOOD

The Food and Drug Administration (FDA), U.S. Department of Health and Human Services (formerly Health, Education and Welfare) and the U.S. Department of Agriculture (USDA) have continuously monitored pesticide residues in foods and animal feeds during three Federal programs (Duggan et al., 1983). These programs include the FDA Total Diet Program (which sampled ready-to-eat foods), the FDA Monitoring Program (which examined raw agricultural commodities, both domestic and imported) and the USDA National Residue Program (which examined red meats and poultry). During the fiscal years 1970-1976, only one stirofos residue was detected, and that was in the fruit food class (Duggan et al., 1983).

The U.S. Department of Agriculture has reported that no stirofos was detected in 1980 in nine liver samples or in one sample of fat from food-producing animals (IARC, 1983).

Ivey et al. (1968) sprayed topical applications of stirofos to cattle to determine residue levels in body tissues of the cattle. Concentrations of 0.125, 0.25 and 0.5% were applied. Most of the small amount of stirofos residues found in the cattle body tissues were detected in the fatty tissues at a maximum concentration of 0.1 ppm. All traces of stirofos were eliminated in <3 weeks.

3.3. INHALATION

Pertinent data regarding inhalation exposure to stirofos were not located in the available literature cited in the Appendix.

3.4. DERMAL

Pertinent data regarding dermal exposure to stirofos were not located in the available literature cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Stirofos can be absorbed by inhalation (Nishimura et al., 1974), ingestion (Akintonwa and Hutson, 1967) or dermal contact (Nishimura et al., 1974). Pertinent kinetic data regarding rates of uptake were not located in the available literature. That absorption occurs is evident from the toxic manifestation of the chemical when administered by these routes. Absorption of ingested stirofos is undoubtedly rapid, as it was observed to be rapidly metabolized and excreted by rats and dogs (Akintonwa and Hutson, 1967). Within 24 hours of a single gavage dose of 3.3 mg [^{14}C-vinyl]-stirofos in olive oil, rats and dogs excreted, in their urine, 44-78 and 75-85% of the radioactivity administered, respectively. A rat given 1.6 mg of ^{14}C-labeled compound in olive oil by gavage excreted 40% of the administered radioactivity via bile within 24 hours (Akintonwa and Hutson, 1967).

4.2. DISTRIBUTION

Akintonwa and Hutson (1967) observed quantitative (85-102%) elimination via urine and feces of an oral dose (3.3 mg) of radiolabeled stirofos within 4 days in rats. Only traces (~0.5%) of radioactivity were found in skin, hair, carcass and expired gases 4 days after administration.

Whetstone et al. (1966) concluded that the low solubility and partitioning properties of stirofos may limit the penetration and translocation of the compound in mammals. This was based on the following observations: the in vitro effectiveness of stirofos for inhibiting cholinesterase was similar to more toxic phosphates; the rate of metabolism of stirofos was similar to other more toxic organophosphates; inhibition of blood cholinesterase by stirofos increased slowly in marked contrast to the rapid inhibition of the enzyme by other organophosphates; and stirofos has low solubility in water

and organic solvents. Whetstone et al. (1966) observed somewhat greater (9-16% of administered ^{32}P after 7 days) amounts of radioactivity in rat carcass following oral dosing with ^{32}P-stirofos than did Akintonwa and Hutson (1967) following oral dosing with [^{14}C-vinyl]-stirofos.

Ivey et al. (1971) monitored the amount of stirofos residues retained in pig tissues following dermal application of the compound for control of lice. Eight mixed breed pigs were given two spray applications 14 days apart, each consisting of 1 quart of 0.5% stirofos. Seven unsprayed pigs were used as controls. Treated and control pigs were slaughtered 1, 7, 14 and 21 days after the second spray, and their tissues were analyzed for insecticide residues. One day after treatment, the internal fat, subcutaneous fat, skin, muscle, kidney, blood and liver contained 0.08-0.44, 0.03, 0.05-0.06, 0.01-0.04, 0, 0 and 0.07-0.24 ppm stirofos, respectively. At 7 days post-treatment, no residues were detected (i.e., <0.005 ppm) in any of the above tissues.

4.3. METABOLISM

Akintonwa and Hutson (1967) studied the metabolism of a single oral dose of stirofos in dogs and rats. Two male and two female adult beagle hounds were given a gelatin capsule containing 3.3 mg (2.46 µCi/mg) of [^{14}C-vinyl]-stirofos in 1 ml of olive oil. Urine and feces were collected for 4 days. Young (6 animals) male and female (6 animals) Porton rats were given a gavage dose of 3.3 mg (2.46 µCi/mg) of [^{14}C-vinyl]-stirofos in 1 ml olive oil. Urine, feces and exhaled gases were collected for 4 days. One male rat weighing 400 g was given 1.6 mg of the same compound in 1 ml olive oil by gavage. A biliary fistula was installed, and bile was collected for 24 hours.

Dogs excreted an average of >75 and 9% of the administered radioactivity within 24 hours by the urinary and fecal routes, respectively. No unchanged parent compound was found in the urine. Dogs excreted radioactivity in the form of 2-chloro-(2,4,5-trichlorophenyl)vinyl methylhydrogen phosphate (50-60%), 2,4,5-trichlorophenylethanediol glucuronide (15%), 2,4,5-trichloromandelic acid (15%) and aglycones of the above glucuronides (5%).

Rats appeared to excrete radioactivity at a slightly slower rate than dogs. About 44-78% and 4-15% of the administered radioactivity appeared in the 0-24 and 24-48 hour urine, respectively. About 16 and 0.5% of the administered radioactivity was recovered in 4 days from rat feces and expired gases, respectively. About 40% of the radioactivity administered to a single rat was recovered in a 0-24 hour bile sample in the form of [1-(2,4,5-trichloro-phenyl)ethyl-beta-D-gluco-pyranosid]uronic acid. Rats excreted radioactivity in the form of [1-(2,4,5-trichlorophenyl)ethyl-beta-D-glucopyranosid]uronic acid (45%), 2,4,5-trichloromandelic acid (30%), 2,4,5-trichlorophenylethanediol glucuronide (10%), 2-chloro-1-(2,4,5-trichlorophenyl)vinyl methyl hydrogen phos-phate (5%) and aglycones of the above glucuronides (5%). A scheme for the metabolism of stirofos in animals was postulated and is presented in Figure 4-1.

Whetstone et al. (1966) observed the absence of intact stirofos in the urine of rats given a single gavage dose of 1 mg (2.9 μCi) of ^{32}P labeled compound in soybean oil. The metabolites, dimethylhydrogen phosphate, methyl dihydrogen phosphate and a desmethyl moiety of the parent compound, were identified in urine. About 61-82% and 15-25% of the administered radioactivity was recovered within 7 days in the urine and feces of male and female rats, respectively.

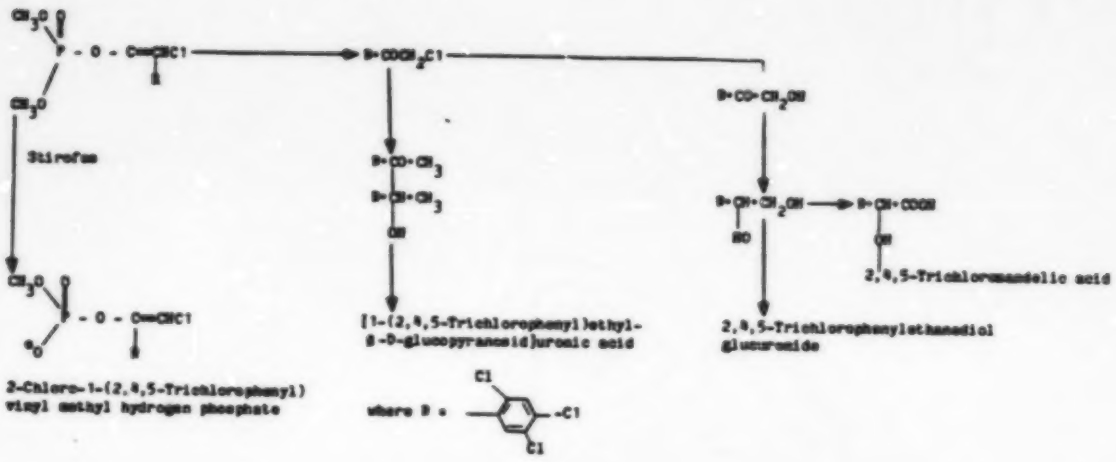

FIGURE 4-1
Possible Metabolic Pathway of Stirofos in Animals
(Akintonwa and Hutson, 1967)

In vitro assays utilizing liver microsomes have been useful in studying the mammalian metabolism of stirofos. Hutson et al. (1972) observed that the glutathione transferases located in the soluble fraction of mouse, rat, rabbit and pig liver microsomes can enzymatically hydrolyze stirofos to a water soluble moiety (i.e., 2-chloro-1-(2,4,5-trichlorophenyl)vinyl methyl hydrogen phosphate). Aktar and Foster (1979) incubated stirofos with the soluble fraction of pig, cow and sheep liver homogenates. They observed that dealkylation of the compound by a reduced glutathione enzyme system was a major pathway of degradation. The rate of dealkylation was most rapid in the cow and sheep. Also observed as degradation products were 2,4,5-trichlorophenacyl chloride, 2,4,5-trichloroacetophenone, 1-(2,4,5-trichlorophenyl) ethanol and 2-chloro-1-(2,4,5-trichlorophenyl)ethanol. Little effect of species type was observed on the rate of degradation to minor metabolites.

4.4. EXCRETION

Stirofos is rapidly excreted as its metabolites by the kidneys of exposed mammals. Lesser amounts of radioactivity from the labeled compound are excreted in feces or expired gases. The relative amounts of radioactivity excreted by the urine and feces may be dependent on the species.

Within 1 day, rats excreted 55-73% and 4-11% of the radioactivity contained in a single gavage dose of ^{32}P-labeled stirofos by the urinary and fecal routes, respectively. Within 7 days, rats excreted 85-97% and 9-16% of the radioactivity contained in a single gavage dose of ^{32}P labeled stirofos by the urinary and fecal routes, respectively (Whetstone et al., 1966).

Rats excreted ~44-78% of the radioactivity contained in a single gavage dose (3.3 mg, 2.46 μ Ci/mg) of [^{14}C-vinyl]-stirofos within 1 day.

Within 4 days of administration, these rats excreted 48-53%, 16% and 0.5% via kidneys, feces and exhalation, respectively. Within 24 hours, dogs excreted 77 and 9% of similar doses by the urinary and fecal routes, respectively (Akintonwa and Hutson, 1967).

5. EFFECTS

5.1. CARCINOGENICITY

NCI (1978) maintained groups of 50 male and 50 female weanling B6C3F1 mice on diets containing 0 (pooled controls), 8000 or 16,000 ppm technical grade tetrachlorvinphos (stirofos) for 80 weeks. It was stated that the purity of the compound was ≥94%, of which 98% was the cis isomer. Additional matched control groups of 10 males and 10 females were included. All surviving animals were observed for an additional 12 weeks before sacrifice and histopathological evaluation. A variety of tumors were observed in control and treated mice at incidence rates which were not statistically different. The incidence of hepatocellular carcinomas in male mice was 0/9, 5/49, 36/50 and 40/50 in the groups receiving 0 (matched control), 0 (pooled control), 8000 and 16,000 ppm tetrachlorvinphos, respectively. The incidence of neoplastic nodules in the livers of female mice was 0/9, 1/48, 14/49 and 9/47 in the groups receiving 0 (matched control), 0 (pooled control), 8000 and 16,000 ppm tetrachlorvinphos, respectively. The incidence of both hepatocellular carcinomas in males and neoplastic nodules in females showed a dose-related trend by the Cochran-Armitage test and were significantly elevated above the matched controls in both dose groups as indicated by the Fisher exact test.

NCI (1978) maintained groups of 50 male and 50 female weanling Osborne-Mendel rats on diets containing 8000 or 16,000 ppm tetrachlorvinphos for 5 weeks, followed by 75 weeks on diets containing 4000 or 8000 ppm tetrachlorvinphos, respectively. The 80-week TWA doses were 4250 and 8500 ppm, respectively. After an observation period of 31 additional weeks, surviving rats were killed and evaluated histopathologically. Control groups consisted of 10 males and 10 females (matched), and 55 males and 55 females

(pooled), which received identical treatment except for inclusion of the insecticide in the diet.

The incidence of C-cell adenoma of the thyroid in females was 1/46, 2/50 and 7/46 in groups receiving 0 (pooled), 4250 and 8500 ppm tetrachlorvinphos, respectively. The incidence of adrenal cortical adenomas in females was 0/50, 2/49 and 5/50 in groups receiving 0 (pooled), 4250 and 8500 ppm tetrachlorvinphos, respectively. The Cochran-Armitage test demonstrated a significant dose-related trend for both tumor types and the increased incidences in the high-dose group were statistically significant as compared to controls by the Fisher exact test. Other tumors and comparisons were not statistically significant.

Walker et al. (1972) maintained groups of 25 male and 25 female weanling Porton rats on diets containing 5, 25, 125 or 2000 ppm tetrachlorvinphos (trans-isomer, 95% pure) for 24 months. Control groups consisted of 45 male and 45 female Porton rats. The incidence of tumors in control and treated groups was not significantly different.

5.2. MUTAGENICITY

Bacterial mutagenicity assays have been ineffective in demonstrating the genotoxic potential of stirofos (Table 5-1). Weak mutagenic activity was reported in cultured human lymphocytes by Kurinnyi and Pilinskaya (1977). Increased metaphase chromosomal aberrations were observed at a stirofos concentration of 2.7×10^{-4} M. Stirofos reportedly induced unscheduled DNA synthesis in human embryo fibroblasts, but experimental details were not provided in the available abstract (Benigni and Dogliotti, 1980).

Only one <u>in vivo</u> mutagenicity assay was available for review (Kurinnyi, 1975). This abstract indicated a negative effect of stirofos on mouse bone marrow chromosomal aberrations when administered by intraperitoneal injection at a dose of 100 mg/kg.

TABLE 5-1

Mutagenicity Data for Stirofos

Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA1535, TA1536, TA1537 and TA1538	spot test	0.02 mg/disc	NR	-	NC	Shirasu, 1976
Reverse mutation	S. typhimurium TA98, TA100	plate incorporation	<3 µmole/ plate	+ mouse liver S-9	-	NC	Bartsch et al., 1980
Reverse mutation	Escherichia coli WP2 try-	plate incorporation	NR	none	-	NC	Nagy et al., 1975
Reverse mutation	E. coli WP2 try$^-$	plate incorporation	NR	none	-	NC	Dean, 1972
Growth inhibition	Bacillus subtilis (H17 Rec$^+$ and M45 Rec$^-$)	spot test (paper disc)	0.02 mg/disc	none	-	NC	Shirasu et al., 1976
Growth inhibition	B. subtilis (H17 Rec$^+$ and M45 Rec$^-$)	spot test (paper disc)	NR	NR	-	NC	Shirasu, 1975
Unscheduled DNA synthesis	EUE human embryo fibroblasts	NR	NR	NR	+	NC	Benigni and Dogliotti, 1980
Chromosome aberrations	cultured human lymphocytes	NR	2.7×10^{-4} M	NR	+	increased metaphase chromosome aberrations (1.7% in control, 4% in treated cells)	Kurinnyi and Pilinskaya, 1977
Chromosome aberrations	mouse bone marrow	intraperitoneal	100 mg/kg	NA	-	NC	Kurinnyi, 1975

NR = Not reported

NC = No comment

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of stirofos were not located in the available literature cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Miller and Gordon (1973) maintained Holstein cows on diets containing 26, 36, 81 or 189 ppm 2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate throughout gestation. No effects of compound administration were observed on reproduction or health of delivered calves. Residues of the insecticide were occasionally found in milk samples (<0.014 ppm), but were generally not detectable (<0.005 ppm).

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Ward et al. (1979) reported on the histopathological results of the NCI (1978) carcinogenicity bioassay. Chronic dietary administration of stirofos caused liver cancer in mice, as well as many non-neoplastic lesions. The incidence of nonneoplastic hepatocellular lesions was concomitant with the incidence of hepatocellular neoplasms. Non-neoplastic hepatic changes included hepatocellular degeneration, increased amounts of reticulin and collagen fibers, and focal accumulation of macrophages and lymphocytes in sinusoids.

In rats chronically exposed to stirofos in the diet, there was an induction of granulomatous disease of the liver (NCI, 1978). The incidence of granulomatous lesions of the liver in male rats was 0/10, 2/50 and 14/46 in the 0.0 (matched controls), 4250 and 8500 ppm groups, respectively. In females, the incidence of granulomatous lesions of the liver was 0/10, 10/49 and 38/40 in the 0.0 (matched controls), 4250 and 8500 ppm groups, respectively.

Walker et al. (1972) studied the subchronic and chronic toxicity of stirofos in rats and dogs. Groups of 12 male and 12 female Porton rats were maintained for 13 weeks on diets containing 12.5, 50, 200, 800 and 3160 ppm stirofos. Untreated controls consisted of 24 male and 24 female rats. No effects attributable to stirofos treatment were observed on hematological values or gross and microscopic histopathology. The 3160 ppm treatment group had inhibited brain and plasma cholinesterase activity, increased liver and kidney weights and reduced growth rates (in females only). Rats treated with 800 ppm stirofos had reduced female growth rates in females and plasma cholinesterase inhibition in males and females. No effects on the above parameters were observed in other treatment groups (Walker et al., 1972).

Groups of three male and three female dogs of unknown strain were maintained for 13 weeks on diets containing 50, 200, 800 and 3200 ppm stirofos. Untreated controls consisted of six male and six female dogs. No effects attributable to stirofos treatment were observed on brain or erythrocyte cholinesterase activity, organ weight changes or gross and microscopic histopathology. The 3200 ppm treatment group had decreased plasma cholinesterase activity, decrease in body weight after 6 weeks, reduced hemoglobin and erythrocyte counts (in males), and increased leucocyte counts. The 800 ppm treatment group had reduced plasma cholinesterase activity, but no other adverse effects. No effects on the above parameters were observed in other treatment groups (Walker et al., 1972).

Groups of 25 male and 25 female Porton rats were maintained for 2 years on diets containing 5, 25, 125 and 2000 ppm stirofos (Walker et al., 1972). Untreated controls consisted of 45 male and 45 female rats. Administration of diets containing 2000 ppm of stirofos for 2 years increased the liver

weights and decreased the kidney weights of females and males, respectively. The incidence of various lesions involving renal, hepatic and cardiac tissue was observed to be similar in all groups. The liver weights of female rats given 125 ppm stirofos were increased compared to controls. Two years of stirofos administration had no other effects on any groups except for reduced plasma cholinesterase activity in males at 2000 ppm and reduced plasma and erythrocyte cholinesterase activity, reduced serum total protein and reduced serum urea in females at 2000 ppm.

5.6. OTHER RELEVANT INFORMATION

Rider and Puletti (1969) administered up to 15 mg stirofos/day to human volunteers, and observed no effect on the cholinesterase activity of erythrocytes or plasma. No further details were located in the available abstract.

Acute intoxication of with stirofos has been observed to cause cholinesterase inhibition. Dermal application (2500 mg/kg) and oral administration (60-100 mg/kg) of a single dose of stirofos was observed to cause a transient reduction in blood cholinesterase of 57 and 59%, respectively (Bolotnyi, 1972). Bolotnyi (1975) demonstrated that inhalation exposure to atmospheres containing stirofos by rats resulted in toxic effects at levels of 9.2 mg/m^3 and inhibited cholinesterase activity by 19% at a concentration of 1.9 mg/m^3.

Acute lethal data for different routes of administration are presented in Table 5-2.

TABLE 5-2

Acute Lethal Data for Stirofos*

Sex	Species	Route	LD_{50} (mg/kg)
Male	rat	oral	4,000
Female	rat	oral	9,100
Male	rat	intraperitoneal	1,160
Female	rat	intraperitoneal	1,450
Male	rat	subcutaneous	>15,000
Female	rat	subcutaneous	>15,000
Male	rat	dermal	>10,000
Female	rat	dermal	>10,000
Male	mouse	oral	4,200
Female	mouse	oral	17,000
Male	mouse	intraperitoneal	1,170
Female	mouse	intraperitoneal	1,410
Male	mouse	subcutaneous	16,000
Female	mouse	subcutaneous	15,000
Male	mouse	dermal	>7,500
Female	mouse	dermal	>10,000

*Source: Nishimura et al., 1974

6. AQUATIC TOXICITY

Data on the toxicity of stirofos to aquatic organisms were limited to median lethal levels determined in three freshwater fish. Johnson and Finley (1980) reported a 96-hour LC_{50} value of 0.43 mg/ℓ in the rainbow trout, Salmo gairdneri. In tests with a 75% wettable powder of stirofos, 96-hour LC_{50} values for bluegill sunfish, Lepomis macrochirus, and channel catfish, Ictalurus punctatus, were 0.53 and >0.50 mg/μℓ respectively (Johnson and Finley, 1980).

Pertinent data regarding the toxicity of stirofos to other aquatic animal or plant species or the accumulation and persistence of residues in aquatic organisms and sediment were not located in the available literature cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

According to an abstract from the Russian literature, Bolotnyi (1975) recommended that 1 mg/m^3 be considered as the Maximum Permissible Concentration for occupational exposure.

The U.S. EPA allows the use of stirofos as a feed additive for control of fecal flies in cattle, horses (at 0.07 g/100 lbs/bw) and swine (0.05 g/100 lb/bw) (Code of Federal Regulations, 1982). Tolerances for residues in or on raw agricultural commodities range from 0.1 ppm for peaches and eggs to 10 ppm on certain fruits and grain, and up to 110 ppm on alfalfa and corn fodder and forage (Code of Federal Regulations, 1973).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of stirofos were not located in the available literature cited in the Appendix.

8. RISK ASSESSMENT

Chronic administration of high concentrations of stirofos causes dose-related adverse effects on the livers of treated mice (Ward et al., 1979) and rats (NCI, 1978). The induction of liver tumors in mice occurred in a dose-related fashion. Increased incidences of C-cell adenoma of the thyroid were observed in rats treated with stirofos.

The ability of stirofos to induce mutation has not been demonstrated in bacterial and in vivo assays; however, two assays using cultured human cells have provided evidence for the mutagenicity of stirofos (Kurinnyi and Pilinskaya, 1977; Benigni and Dogliotti, 1980). The data available on the mutagenic potential of stirofos are too limited for any definitive conclusions.

IARC (1983) evaluated animal experiments regarding the tumorigenicity of stirofos and determined that limited evidence of the carcinogenicity of stirofos to experimental animals is available.

NCI (1978) provides dose-response data for the induction of hepatocellular carcinoma in mice and C-cell adenoma of the thyroid in rats. The incidence of hepatocellular carcinomas in male mice fed stirofos in the diet for 560 days and observed for an additional 84 days was 0/9, 5/49, 36/50 and 40/50 in the matched controls, pooled controls, 8000 ppm group and 16,000 ppm group, respectively. The corresponding incidence of adenomas and carcinomas combined are 0/9, 8/49, 47/50 and 42/50. Using these data, a q_1^* can be calculated for humans. The dietary levels are equivalent to transformed doses of 0, 0, 904 and 1809 mg/kg/day, respectively. These transformed doses are obtained by assuming that mice consume food at a rate of 13% of their body weight per day, and by expanding the length of exposure

(560 days) to the length of the experiment (644 days) (Federal Register, 1980). From these data, the upper bound estimates for the carcinogenic potency of stirofos are calculated as $q_1^* = 2.42 \times 10^{-2}$ $(mg/kg/day)^{-1}$ for hepatocellular carcinomas alone and $q_1^* = 8.02 \times 10^{-2}$ $(mg/kg/day)^{-1}$ for adenomas and carcinomas combined. The values were calculated using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (Federal Register, 1980). While the combined tumor data give a higher potency value, the data have a peculiar response pattern that suggests that time-to-tumor analysis is warranted. Sufficient information is not accessible for this analysis. Given this situation, the potency value of 2.42×10^{-2} $(mg/kg/day)^{-1}$ is preferred recognizing that a different value may result from further analysis of the tumor data. The conversion factor used in the calculation of this q_1^* for humans (assuming 70 kg body weight) from animal data was the cube root of the body weight ratio (Federal Register, 1980).

Complete data for the derivation of the q_1^* are presented in Appendix B. The q_1^* derived above was based upon a study conducted by Gulf South Research Institute under contract to NCI (1978). The results of some of the bioassays conducted by Gulf South Research Institute have been called into question by the National Toxicology Program (NTP, formerly NCI) (Cooper, 1983). The bioassay on stirofos has not been questioned by NTP.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal studies with stirofos, but no additional carcinogenicity data were available. Hence, no change in the risk assessment is necessary.

9. REFERENCES

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APPENDIX A

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in November, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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APPENDIX B

Cancer Data Sheet for Derivation of q_1^*

Compound:	stirofos (tetrachlorvinphos)
Reference:	NCI, 1978
Species, Strain, Sex:	mouse, C6B3F1, male
Body Weight:	0.03 kg (measured)
Length of Exposure (l_e) =	560 days
Length of Experiment (L_e) =	644 days
Lifespan of Animal (L) =	730 days
Tumor Site and Type:	adenomas/carcinomas combined
Route, Vehicle:	oral, diet

Experimental Doses or Exposures	Transformed Dose mg/kg/day	Incidence of Carcinomas No. Responding/ No. Tested (or Examined)	Incidence of Adenomas/Carcinomas Combined/No. Tested (or Examined)
0 ppm (pooled control)	0	5/49	8/49
8,000 ppm x 0.13 x 560/644 =	904	36/50	47/50
16,000 ppm x 0.13 x 560/644 =	1809	40/50	42/50

1. Unadjusted q_1^* from study = 1.25533×10^{-3}; human q_1^* = 2.42×10^{-2} $(mg/kg/day)^{-1}$ when incidence of carcinomas is used.

2. Unadjusted q_1^* from study = 4.15×10^{-3}; human q_1^* = 8.02×10^{-2} $(mg/kg/day)^{-1}$ when incidence of adenomas/carcinomas is used.

3. Due to lack of goodness of fit, the combined data from the high dose group are excluded from the combined tumor calculation.

4. The pooled control is used in these calculations. The use of the matched controls would only increase the potency estimate by ~4%.